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ENHANCEMENT OF SOLUBULITY OF PROPIOMAZINE BY PELLETIZATION

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ABSTRACT

The present search engrossed on the preparation and evaluation of delayed release pellets of Propiomazine using a different grade of polymers like HPMC 5CPS, PEG 6000 as a sustained released polymer. Propiomazine is an antihistamine blocking H1 receptors, it is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. pellets are multiparticulate dosage form which was formed by the agglomeration of fine powdered excipient and drugs together that leads to the formation of small free flowing spherical or semi spherical particles. The result of the pellets were within the limits which indicated good flow potential for the prepared pellets. Drug-loaded pellets exhibited spherical shape with uniform and smooth coating. Based on the result, Trail 8 coating level formulations are suitable for the successful delivery of the drug into the lower part of intestine and colon. From the present work, it can be concluded that the prepared drug delivery system can be used for Propiomazine drug.

KEYWORDS: Propiomazine, pellets.

INTRODUCTION

Pellets are small free flowing, spherical particulate, manufactured by the agglomeration of fine powder or granules.[1]

In recent years, there has been a growing interest in the field of pelletization to produce spherical pellets which can be changed into several dosages forms like tablet and capsule or can be administered as such. Pelletization involves size enlargement process and if the final

agglomerates are spherical in shape in the size range of 0.5-2.0 mm, they are called pellets 2, 3, 4. Pellets have numerous therapeutic as well as technical advantages such as enhanced drug absorption due to involvement of large GI surface in absorption process, less gastric irritation by limiting localized buildup and dose dumping, good flow ability due to uniform size and shape, high tensile strength, low friability, narrow particle size distribution, and uniform packing characteristics.[2-6]

The pelletized products can improve the safety and efficacy of the active agent. The pellets are directly filled into capsule and can also be compressed into tablets. The compression of pellets into tablets is much more ideal than enclosing them in a hard gelatin capsule.[7] In multiple-unit systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. Manufacturing of pellets using layering process such as solution layering, suspension layering or powder layering and extrusion-spheronization process have been used over the years. These processes have major limitation such as use of granulating liquid which causes stability problems during processing and storage. In recent years hot melt extrusion and freeze pelletization have been used to produce spherical pellets without the use of water.[8]

The word pellet is used to describe a variety of systematically product geometrically defined agglomerates obtained from diverse starting material. In the pharmaceutical industry, pellets can be defined as agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration.2 It consist of small discrete unit and exhibit some derived characteristics produced by agglomeration of fine powder with binder solution normally the size of the pellets varies from 0.5 – 1.5 mm for oral dosage form.

- Improve aesthetic appearance of products.
- Achieve control release rate of drugs when coated with polymers.
- Improve flow properties and flexibility in formulation development and manufacturing.
- It has less variance in transient time through the gastro intestinal tract (GIT) than a single unit dosage form like tablet.[8]

Application of spherical crystallization in pharmaceuticals

- For increasing solubility and dissolution rate of poorly soluble drug.
- For masking bitter taste of drug.

- Improve flow ability and compressibility.
- Reduces cost of production.

Pellets can be defined as small, free flowing, spherical particulates manufactured by the agglomeration o fine powder and granules of drug substances and excipients typically from about 0.5mm to 1.5mm, by using appropriate processing equipment.8 The pelletized products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. In multiple-unit systems, the total drug dose is divided over many units. Failure of a few units may not be as consequential as failure of a single-unit system. This is apparent in sustained release (SR) single unit dosage forms, where a failure may lead to dose dumping of the drug.

Pelletization

Pellets can be prepared by a special technique called Pelletization. This technique is referred to an agglomeration process that convert fine powder or granules of bulk drug or excipient in to small , free flowing , spherical or semi spherical pellets .This technique is needed to produce pellets of uniform size with high drug loading capacity and also prevent segregation and dust.[11]

Advantages of Pelletization Technique[11]

- ✓ When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
- ✓ Pellets are recommended for patients with difficulty in swallowing and dysphasia like in case of children and aged people.
- ✓ Pelletization reduces intra and inters subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
- ✓ Pelletization produces spheroids with high loading capacity of active ingredient without producing extensively large particles.
- ✓ Pellets exhibit better roundness than the commercial non-pareil seeds and have excellent flow and packing properties.
- ✓ Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.

- ✓ Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
- ✓ Pellets reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the drug bioavailability.
- ✓ Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.
- ✓ Particles less than 2-3 mm rapidly pass the pylorus regardless of the filling level of the stomach or the size and density of chyme. Also, GI irritations are limited spread as the particles spread in the intestine.

Propiomazine is an antihistamine blocking H1 receptors. It is used to treat insomnia, and to produce sleepiness or drowsiness and to relieve anxiety before or during surgery or other procedures and in combination with analgetics also during labor. Propiomazine is a phenothiazine, but is not used as a neuroleptic because it does not block dopamine receptors well.

Propiomazine, an atypical antipsychotic agent, is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. Future uses may include the treatment of obsessive-compulsive disorder and severe behavioral disorders in autism. Structurally and pharmacologically similar to clozapine, propiomazine binds to alpha(1), dopamine, histamine H1, muscarinic, and serotonin type 2 (5-HT2) receptors.[12-14]

The aim of the present research was mainly concentrated on the formualtion and evaluation of sustained release pellets of Propiomazine with different concentrations of HPMC 5cps.

MATERIALS AND METHODS

Propiomazine was obtained as gift sample from RA Chem Pharma, Nacharm, Hyderabad, India. HPMC 5CPS was obtained as gift samples from Dow Chemical's Asia pvt. Ltd., Mumbai. PEG 6000, Drug Coat E 100, Polysorbate 80, Iso Propyl Alcohol, Micro cristalline cellulose were obtained from Loba chemi Pvt. Ltd., Mumbai.

METHODS

Table 1: Formulation Chart of Propiomazine Pellets Preparation.

	Trial 1 (1.5 kg)		Trial 2 (1.5 kg)		Trial 3 (1.5 kg)		Trial 4(1.5 kg)		Trial 5(1.5 kg)		Trial 6(1.5 kg)		Trial 7(1.5 kg)		Trial 8(1.5 kg)	
Ingredients	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**	**%w/w**	**Quantity (grams)**
Micro cristalline cellulose (pellets)	72	1080	62	930	52	780	52	780	52	780	52	780	52	780	52	780
Propiomazine	21	315	21	315	21	315	21	315	21	315	21	315	21	315	21	315
HPMC 5CPS	4	60	14.2	213	24.2	363	23.2	348	23.2	348	23.2	348	23.2	348	22.2	333
peg 6000	1	15	0.8	12	0.8	12	0.8	12	0.4	6	0.2	3	0.6	9	0.8	12
Drug Coat E 100	2	30	2	30	2	30	3	45	3	45	3	45	3	45	4	60
Polysorbate 80									0.4	6	0.6	9	0.2	3		
Iso Propyl Alcohol	Q.S		Q.S		Q.S		Q.S		Q.S		Q.S		Q.S		Q.S	
Water	Q.S		Q.S		Q.S		Q.S		Q.S		Q.S		Q.S		Q.S	

Formulation Chart

Batch Size – 1.5 kg

Drug Layering Solution Preparation

Step 1. Add the dispensed quantity of HPMC E5 (Hypromellose) to required quantity of Iso propyl alcohol with continuous stirring to get a clear dispersion.

Step 2. Dissolve weighed quantity of Propiomazine to required quantity of Iso propyl alcohol with continuous stirring until clear solution is obtained.

Step 3. Add step 1 dispersion to dispensed quantity of water with continuous stirring until clear solution obtained.

Step 4. Add step 2 solution to step 3 solution with continous stirring to get clear solution.

Step 5. Dispensed quantity of plasticizer/plasticizers added to to step 4 solution with continous stirring to get final clear drug loading solution.

Note: The ratio of solvents (Isopropyl alcohol: water) taken was 70:30 and the concentration of solids in the solution was 6%.

Evaluation

Dissolution Parameters

Apparatus – Paddle.

RPM – 100.

Medium - SGF without enzyme(pH1.2 buffer).

Volume - 900 mL.

Time points - 5,10,15,20,30,45,60,90 & 120 min, infinity.

Analysis by- UV.

% ASSAY

The amount of drug in Pellets was important for, and batch to batch is to evaluate for efficacy of Pellets. For this test, take Pellets from each batch were weighed and powdered. Weighed equivalent to the average weight of the Pellets powder and transferred into a 100 ml of volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by HPLC.

RESULT AND DISCUSSION

Table 2: % **Drug Release study of formulated Trial 1.**

Dissolution	Trial 1			
Time in minutes	%Avg	%Min	%Max	%RSD
5	2.0	2.0	3.0	10.6
10	3.0	3.0	3.0	6.7
15	4.0	4.0	5.0	6.6
20	5.0	5.0	6.0	6.5
30	7.0	6.0	8.0	6.4
45	9.0	7.0	9.0	7.4
60	9.0	9.0	10.0	3.4
90	10.0	10.0	11.0	4.2
120	11.0	10.0	11.0	3.3
infinity	11.0	11.0	12.0	3.5

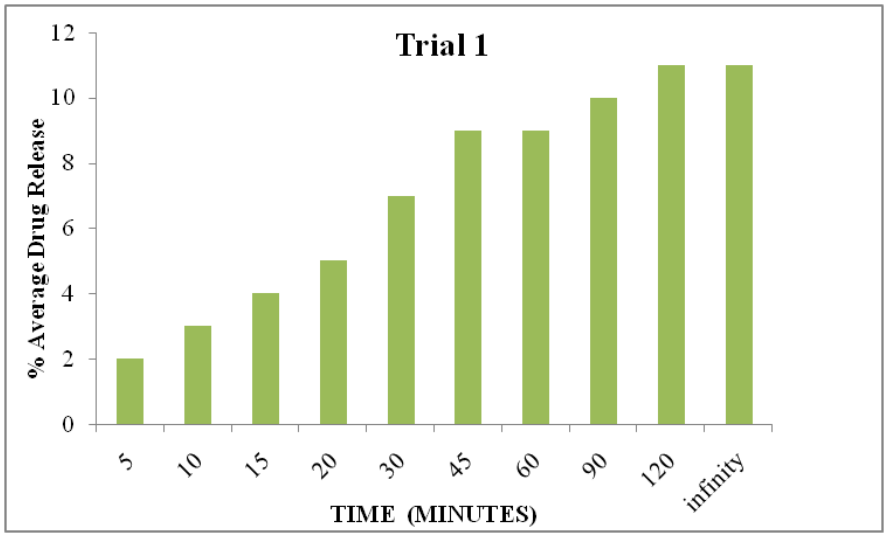

Fig. 1: Trial 1 Dissolution graph.

Formulation of pellets by using HPMC 5CPS 4% w/w trial 1 showed good drug release 11.0 in 120 min. and % of RSD was found to be 3.5.

Table 3: % Drug Release study of formulated Trial 2.

Dissolution	Trial 2			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	1.0	1.0	1.0	6.3
10	2.0	2.0	2.0	2.3
15	3.0	3.0	3.0	0.7
20	4.0	4.0	4.0	3.0
30	6.0	6.0	6.0	1.0
45	8.0	8.0	8.0	2.2
60	9.0	9.0	10.0	3.2
90	13.0	13.0	13.0	0.8
120	16.0	16.0	18.0	0.5
infinity	18.0	18.0	18.0	0.7

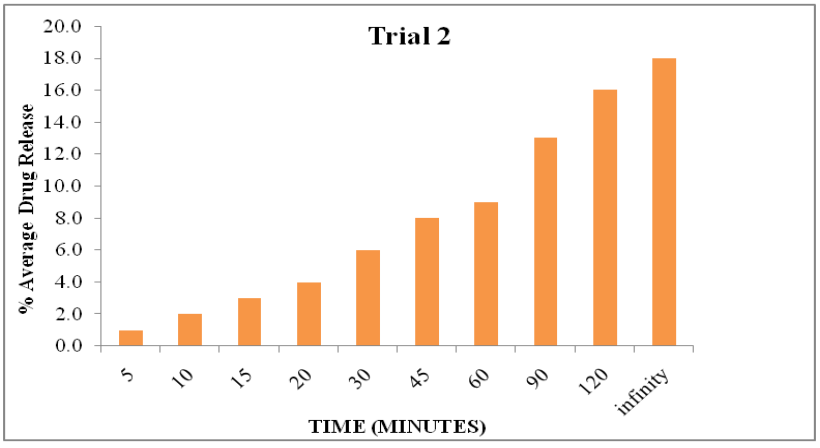

Fig 2: Trial 2 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (213 gm), peg 6000 (12 gm) trial 2 showed maximu, drug release 18.0 in 120 min. and % of RSD was found to be 0.7

Table 4: % Drug Release study of formulated Trial 3.

Dissolution	TRIAL 3			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	1.0	0.0	1.0	59.3
10	2.0	2.0	3.0	23.5
15	4.0	3.0	4.0	8.0
20	6.0	6.0	7.0	6.6
30	9.0	9.0	10.0	5.3
45	13.0	12.0	13.0	2.9
60	16.0	15.0	17.0	4.8
90	21.0	20.0	22.0	3.0
120	25.0	24.0	26.0	2.4
infinity	27.0	26.0	30.0	5.1

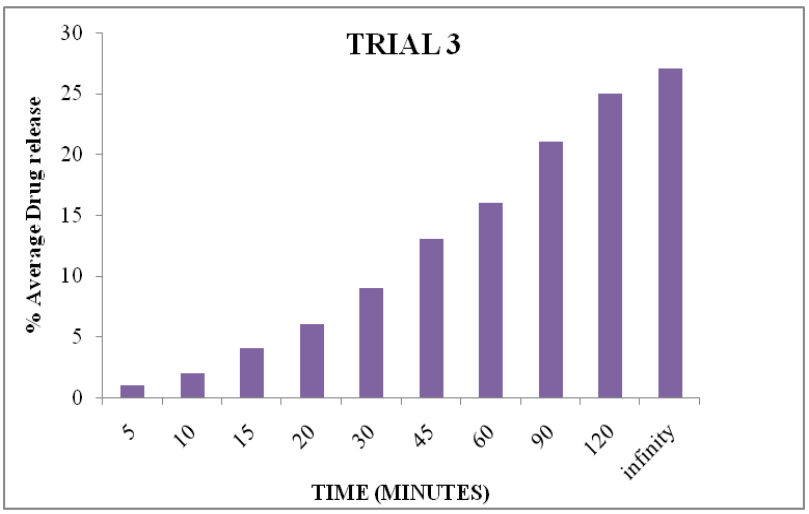

Fig. 3: Trial 3 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (363 gm), peg 6000 (12 gm) trial 3 showed maximu, drug release % Avg 27.0 in 120 min. and % of RSD was found to be 5.1.

Table 5: % Drug Release study of formulated Trial 4.

Dissolution	TRIAL 4			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	3.0	3.0	3.0	0.0
10	5.0	4.0	6.0	21.7
15	9.0	8.0	10.0	12.4
20	12.0	10.0	13.0	14.4
30	18.0	16.0	19.0	9.6
45	25.0	23.0	27.0	9.4

60	31.0	29.0	33.0	7.0
90	42.0	39.0	43.0	5.8
120	51.0	48.0	52.0	4.9
infinity	58.0	55.0	60.0	3.9

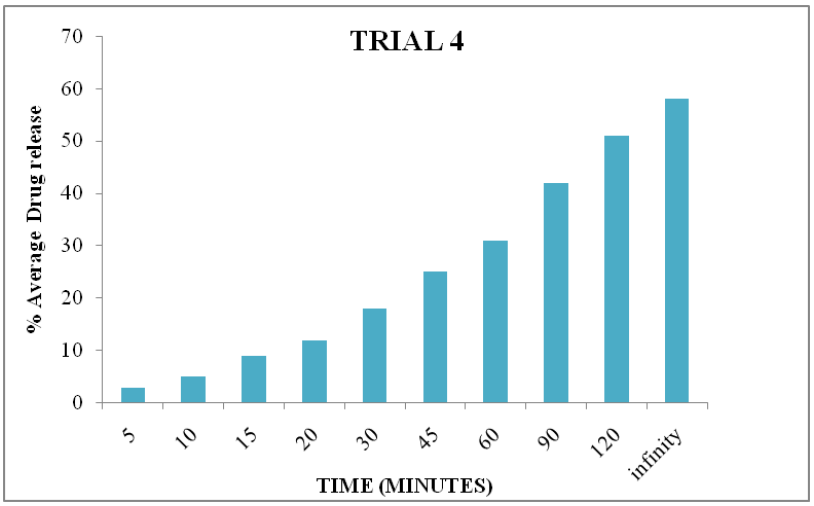

Fig. 4: Trial 4 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (348 gm), peg 6000 (12 gm) trial 4 showed drug release % Avg 58.0 in 120 min. and % of RSD was found to be 3.9.

Table 6: % Drug Release study of formulated Trial 5.

Dissolution	Trial 5			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	3.0	3.0	3.0	0.0
10	5.0	4.0	6.0	21.7
15	9.0	8.0	10.0	12.4
20	12.0	10.0	13.0	14.4
30	18.0	16.0	19.0	9.6
45	25.0	23.0	27.0	9.4
60	31.0	29.0	33.0	7.0
90	42.0	39.0	43.0	5.8
120	51.0	48.0	52.0	4.9
infinity	58.0	55.0	60.0	3.9

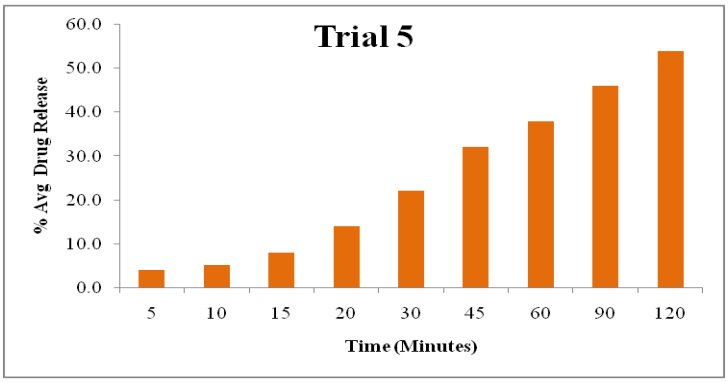

Fig 5: Trial 5 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (348 gm), peg 6000 (6 gm) trial 5 showed drug release % Avg 58.0 in 120 min. and % of RSD was found to be 3.9.

Table 7: % Drug Release study of formulated Trial 6.

Dissolution	TRIAL 6			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	2.0	1.0	3.0	32.1
10	5.0	4.0	5.0	10.9
15	9.0	7.0	13.0	30.1
20	15.0	11.0	21.0	25.1
30	23.0	17.0	29.0	17.6
45	33.0	29.0	35.0	7.0
60	39.0	36.0	41.0	4.8
90	48.0	44.0	52.0	5.9
120	58.0	53.0	62.0	5.7
infinity	64.0	62.0	66.0	1.8

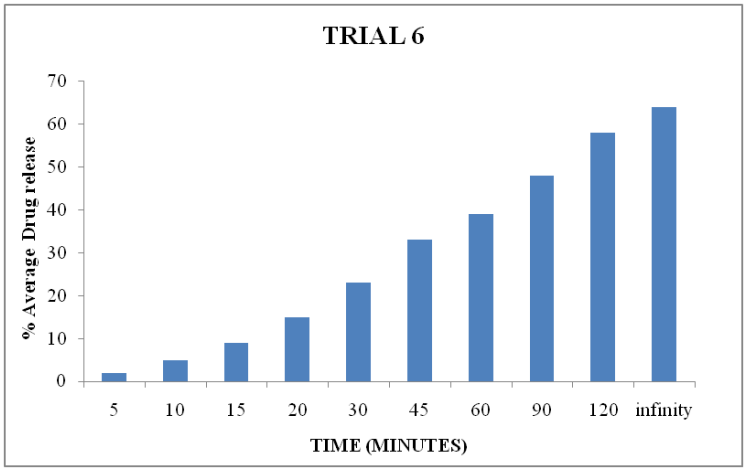

Fig. 6: Trial 6 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (348 gm), peg 6000 (3 gm) in this decrease the concentration of peg 6000 increase the drug release trial 6 showed drug release % Avg 64.0 in 120 min. and % of RSD was found to be 1.8

Table 8: % Drug Release study of formulated Trial 7.

Dissolution	TRIAL 7			
Time In Minutes	% Avg	%Mean	% Max	% RSD
5	3.0	3.0	3.0	0.0
10	5.0	4.0	6.0	21.7
15	9.0	8.0	10.0	12.4
20	12.0	10.0	13.0	14.4
30	18.0	16.0	19.0	9.6
45	25.0	23.0	27.0	9.4

60	31.0	29.0	33.0	7.0
90	42.0	39.0	43.0	5.8
120	51.0	48.0	52.0	4.9
infinity	58.0	55.0	60.0	3.9

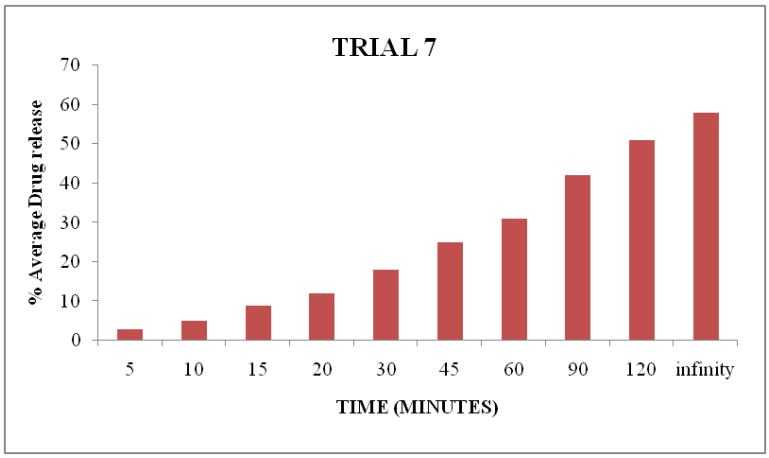

Fig. 7: Trial 7 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (348 gm), peg 6000 (9 gm) in this increase the concentration of peg 6000 increase the drug release trial 7 showed drug release % Avg 58.0 in 120 min. and % of RSD was found to be 3.9.

Table 9: % Drug Release study of formulated Trial 8.

Dissolution	TRIAL 8			
Time In Minutes	% Avg	%Min	% Max	% RSD
5	9.0	7.0	11.0	22.3
10	35.0	34.0	36.0	2.3
15	53.0	51.0	55.0	4.4
20	64.0	61.0	66.0	4.5
30	75.0	72.0	78.0	4.3
45	83.0	80.0	86.0	2.5
60	88.0	85.0	90.0	2.5
90	92.0	90.0	94.0	1.8
120	94.0	93.0	96.0	1.2
infinity	94.0	93.0	96.0	1.2

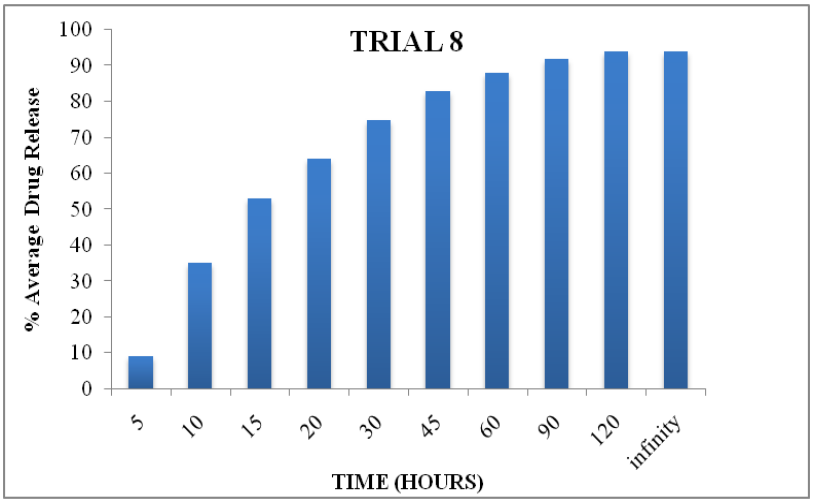

Fig. 8: Trial 8 Dissolution graph.

Formulation of pellets by using HPMC 5CPS (333 gm), peg 6000 (12 gm) in this decrease the concentration of HPMC 5CPS increase the concentration of peg 6000 drug release trial 8 showed drug release % Avg 94.0 in 120 min. and % of RSD was found to be 1.2 . and Trial 8 Optimised Formulation.

Table 10: % Assay of various batches.

S. No.	Trial	%Assay
1	Trial 1	98.67
2	Trial 2	99.54
3	Trial 3	98.43
4	Trial 4	99.78
5	Trial 5	98.41
6	Trial 6	99.65
7	Trial 7	99.24
8	Trial 8	98.56

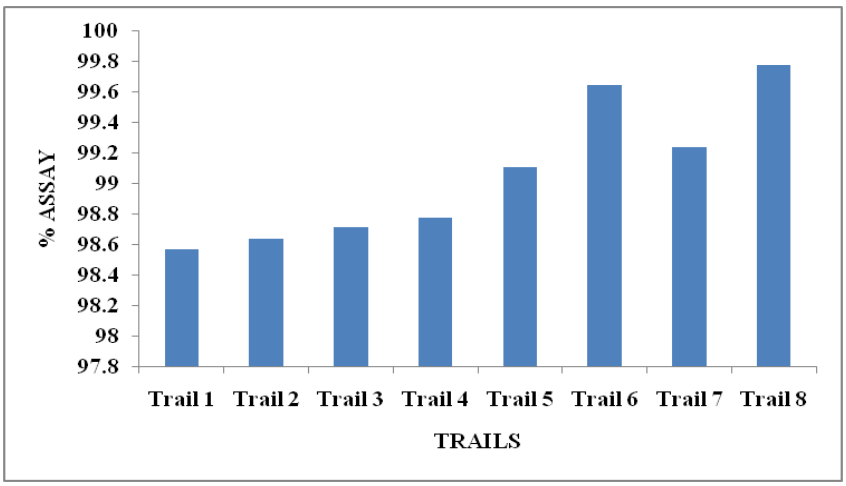

Figure 9: % Assay Graph of various batches.

From above results, Trial 8 Optimised Formulation.

CONCLUSION

Propiomazine, an atypical antipsychotic agent, is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia.

The method employed to prepare Propiomazine pellets were simple, rapid and economical without any use of toxic solvents. The result of the pellets were within the limits which indicated good flow potential for the prepared pellets. Drug-loaded pellets exhibited spherical shape with uniform and smooth coating. Based on the result, Trial 8 coating level formulations are suitable for the successful delivery of the drug with improved solubility and bioavailability. From the present work, it can be concluded that the prepared drug delivery system can be used for Propiomazine drug.

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